REMARKS

Claims 1-17 are currently pending in the application. Claims 1-16 have been withdrawn from consideration by the Examiner as being drawn to a nonelected invention. Claim 18 has been canceled without prejudice. Claim 17 is under consideration.

Information Disclosure Statement

The office action states that neither the parent application 09/077,173 nor the instant application contain the references that have been crossed off from the IDS filed September 7, 2004, and that Applicant must provide those references listed in the IDS but not found in the parent, in order for them to be considered. Applicant submits that a copy of each of these references is contained in a second parent application, 10/753,695, filed Jan. 8, 2004, as evidenced by the attached 1449 form from '695 in which the examiner considered all the references. According to MPEP 609.04, Applicant is not required to provide yet another copy of them.

> 37 CFR 1.98(d) states that a copy of any patent, publication, pending U.S. application, or other information listed in an information disclosure statement is not required to be provided if: (A) the information was previously cited by or submitted to, the Office in a prior application, provided that the prior application is properly identified in the IDS and is relied on for an earlier filing date under 35 U.S.C. 120; and (B) the IDS submitted in the earlier application complies with 37 CFR 1.98(a)-(c). If both of these conditions are met, the examiner will consider the information previously cited or submitted to the Office and considered by the Office in a prior application relied on under 35 U.S.C. 120. MPEP 609.04

If paper copies of the references cited on the 1449 form are not found with the second parent application 10/753,695, please contact the undersigned, and Applicant will provide the missing paper copies.

Claims rejection 35 U.S.C. 101

The rejection of Claim 17 is maintained under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. Applicant respectfully traverses the rejection.

The office action states that there is no guidance on how to use the claimed transgenic mouse which comprises a disruption of its P2Y4 receptor, that it is unclear what treatment of cystic fibrosis by UTP has to do with the claimed mouse that does not exhibit Cystic Fibrosis,

and that it is unclear how administration of the ligand UTP has any biological effect in the claimed mouse that has no P2Y4 receptor.

Applicant has disclosed in the specification that the actions of extracellular nucleotides UTP are mediated by P2Y4 receptors and has asserted in the specification that P2Y4 receptors are a pharmacotherapeutic target for the treatment for cystic fibrosis. Applicant notes the following guidelines for examining an asserted utility:

- In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101. See, e.g., *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (CCPA 1965); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).
- MPEP 2102: As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

The office action acknowledges that Ghanem et al. "substantiates the potential of P2Y4 as a target for the treatment of intestinal complications in cystic fibrosis", and that the post filing date reference Robaye et al. "teach P2Y4 and its role in cystic fibrosis, i.e. a the specific aspect of gastrointestinal". In view of this acknowledgement, Applicant contends the asserted specific role for P2Y4 a pharmacotherapeutic target for the treatment for cystic fibrosis is satisfied.

The office action states further that Ghanem et al. substantiates the potential of P2Y4 as a target for the treatment of intestinal complications. But Applicant notes that these intestinal complications are actual symptoms of the disease, not complications per se. That is, the lung is not the only tissue affected in cystic fibrosis patients, the CFTR receptor altered in cystic fibrosis is normally expressed in additional tissues.

The office action further states that: "the specification does not provide guidance to specifically arrive at cystic fibrosis in the gastrointestinal system", (page 6). Applicant contends that "cystic fibrosis" was well known at the time of the invention to be a disease not limited to a particular tissue, and nothing in the specification suggests limiting the use P2Y4 targets to one particular tissue of cystic fibrosis. Defects in CFTR destroy or reduce the ability of epithelial

cells in the airways, sweat glands, pancreas and other tissues to secrete Cl in response to cAMP-mediated agonists and impair activation of apical membrane channels by cAMP-dependent protein kinase A (PKA). See Frizell et al., Trends Neurosci 10:190 (1987); Welsh, FASEB J. 4:2718 **(1990)**.

The office action states that it is not entirely clear whether the phenotype exhibited by the mice correlate to a human condition, as Robaye et al. also indicate, further states that it remains to be seen whether the P2Y4 knockout mice are a model of the human condition, and concludes that as such, at the time of filing the specification does not clearly indicate a use of the claimed mouse.

MPEP § 2107.02, under the heading "The Claimed Invention Is The Focus Of The Utility Requirement," states

- "...regardless of the category of invention that is claimed (e.g., product or process), an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112; and "
- Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965), and
- Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.

Knockout mice were routinely made and used at the time of filing. In light of the above legal arguments, the post-filing date publications confirming the disclosed assertion that P2Y4 is a target for cystic fibrosis, the post-filing date publications of P2Y4 and P2Y2 knockout mice, and the post filing date publications demonstrating the use of P2Y2 knockout mice as a therapeutic target for cystic fibrosis, Applicant respectfully submits that a transgenic mouse comprising a disruption in the endogenous P2Y4 receptor gene, wherein the disruption of the P2Y4 receptor gene results in the inability of the mouse to produce detectable levels of the P2Y4 receptor, is patentably useful.

Claims rejection 35 U.S.C. 112, first paragraph, enablement

The rejection of Claim 17 is maintained under 35 USC 112, first paragraph as failing to comply with the enablement requirement.

Applicant respectfully traverses.

Predictability

The office action states that it can not reasonably be predicted that the phenotypes exhibited by the knockout mice are related to gene disruption, nor can it be reasonably predicted that the phenotypes exhibited by the mouse are similar to that of a human disease or symptom of a human disease. The Office action cites Doetschmann as teaching that using different strains or cross breeding do not address the issue that an artisan will predictably arrive at a mouse with a readily interpretable phenotype, and concludes that it is unclear what mouse strains are ideal to use such that an artisan readily arrives at a mouse with a phenotype that is related to the disrupted gene. Thus the office action remains concerned with the predictability in arriving at the claimed transgenic mouse.

Applicant notes that the only required limitation of the claim with respect to a specific phenotype is that the mouse be unable to produce a detectable level of P2Y4. This is not a complicated phenotype. Applicant further contends that the technology of making knock out mice was well established at the time of the invention and is an established means if establishing animal models of disease. Applicant submits that the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Applicant further submits that the high developed state of the art regarding knock-out technology in mice, in combination with the identification and sequence of the gene encoding P2Y4 disclosed by Applicant in the specification provides support for a substantial degree of predictability in arriving at the claimed mouse having a phenotype being easily screened for, i.e. an inability to produce a detectable level of P2Y4. The state of the art with respect to the claimed invention governs the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The technology of making knockout mice and methods for screening for those mice which are unable to produce a detectable level of protein

encoded by a target gene as required by claim 17 was well established at the time of the invention in light of the instant specification. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art (Atlas Powder Co. v. E.I. duPont de Nemous & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)). Applicant contends that no more than routine experimentation is required to obtain the claimed mouse which has no detectable level of P2Y4. Applicant further notes that P2Y4 belongs to the family of G coupled protein receptors, of which knock out animals have been successfully produced as early as 1999, see Cressman et al. J Biol Chem, Vol. 274, Issue 37, 26461-26468, September 10, 1999, which describes knockout mice of another purogenic receptor (P2Y2). Thus the specification in combination with art known techniques at the time of filing, provide predictability and thus enablement for the claimed mouse. Further, as discussed below, Applicant notes the MPEP cautions against the reliance of post-filing date developments that enable previously unknown variations to establish nonenablement.

Animal Models

The Office action further states that the use of the claimed knockout mouse as a model of disease or use in an application for human therapy is not clear at the time of filing. Applicant has noted the art accepted use of transgenic mice as animal models of disease, e.g. cystic fibrosis, of record. In MPEP section 2107.03 Special Considerations for Asserted Therapeutic or Pharmacological Utilities, Office personnel are warned to be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application. See *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956) ("The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."); *In re Wooddy*, 331 F.2d 636, 639, 141 USPQ 518, 520 (CCPA 1964) ("It appears that no one on earth is certain as of the present whether the process claimed will operate in the manner claimed. Yet absolute certainty is not required by the law. The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it.").

In light of the above remarks which demonstrate that the claimed mouse is enabled,

Applicant respectfully requests reconsideration and withdrawal of the rejection.

Priority

The office action asserts that Applicant's prior-filed Application Nos. 10/753,695 and 09/077,173 (now patent US 6,790,626) fail to provide adequate support or enablement for a transgenic non-human mammal which has a phenotypic abnormality due to a disruption in a P2Y4 gene. Applicant respectfully traverses.

The instant application is a divisional of . 10/753,695 which is a divisional of 09/077,173 (now patent US 6,790,626), and supported by the same specification. Applicant has demonstrated above that the instant specification supports the enablement for the claimed mouse. As discussed above, Applicant disagrees with the contention presented in the office action that there is unpredictability in arriving at transgenic mice, especially given the simple phenotype of the claimed mouse, i.e. no detectable P2Y4, the well developed technology of making transgenic mice at the time of filing, the existence of P2Y2 knockout mice, the post-filing date publication of P2Y4 knock-out mice by Robaye et al, and the fact that one of the instant inventors is an author of the referenced Robaye et al paper describing the P2Y4 knock-out mice.

Applicant submits that the specification and the art provide guidance for an artisan to arrive at the claimed invention, as described above, and thus the instant application is entitled to the benefit of the afore-mentioned prior-filed Application No. 10/753,695 and 09/077,173 (now patent US 6,790,626). In light of these remarks, Applicant respectfully requests the benefit of Applicant's above referenced prior filed applications.

Claims Rejections – 35 U.S.C. §102

Claims 17 and 18 are rejected under – 35 U.S.C. §102(a) as being anticipated by Robaye et al., (2003), Molecular Pharmacology, 63:777-783.

Applicant respectfully traverses the rejection on the grounds that Robaye et al. is not prior art, given that Applicant claims priority and is entitled to the benefit of Applicant's prior-filed applications Application No. 10/753,695 and 09/077,173 (now patent US 6,790,626), for the reasons discussed supra. Because Robaye et al. is not prior art, the cited reference does not anticipate claim 17.

In light of the amendments and above remarks, Applicant respectfully requests reconsideration of the rejection

Conclusion

Applicant submits that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicant respectfully requests the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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